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Nonocclusive Hemorrhagic Necrosis of the Intestine

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Hemorrhagic intestinal necrosis occurs without demonstrable mechanical obstruction of the mesenteric vascular supply. The etiologic factors include (1) congestive heart failure, (2) cardiac arrhythmia, (3) dehydration, and (4) digitalis therapy with or without digitalis toxicity. All of these factors have been shown to result in a decrease in splanchnic blood flow. The outcome of this disease has invariably been fatal. Early recognition and nonoperative management directed toward increasing splanchnic blood flow are the most significant factors in the survival of patients.

APPROXIMATELY 20 PERCENT of the cases of hemorrhagic intestinal necrosis occur without demonstrable obstruction of the mesenteric arterial or venous blood supply. The occurrence of this condition was first documented in the American literature in 1943 by Thorek.[12] It has been suggested on numerous occasions that nonocclusive hemorrhagic necrosis of the intestine is directly related to congestive heart failure,[1-13] digitalis therapy, and digitalis toxicity.[14-18] Although the clinical and pathologic manifestations are distinctive, the entity remains relatively unknown and the diagnosis is infrequently made, even after diagnostic celiotomy. As a result, the outcome of this disease has invariably been fatal. In this report, a review of the literature is presented, discussing the possible etiologic factors as well as the clinical and pathologic features. The case of a patient with nonocclusive hemorrhagic intestinal necrosis thought to be secondary to digitalis intoxication is also presented as the only known survivor of this condition. Guidelines to the diagnosis and treatment are outlined.

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Report of a Case

A 59-year-old Caucasian woman was admitted to the University of California, Davis, Sacramento Medical Center on March 20, with complaint of severe abdominal pain. Four days before admission she deliberately ingested 30 tablets (3 grams) of digitalis leaf. She had been taking 100 mg digitalis leaf daily, a thiazide diuretic (Naturetin®), 5 mg daily, and potassium chloride supplement for several years because of congestive heart failure. There was no recent history of dyspnea, orthopnea, chest pain, palpitation, or edema. Approximately 25 hours after the overdose, nausea and vomiting occurred. Abdominal pain was not present until the morning of admission, when severe intermittent abdominal cramps were noted.

On physical examination the patient was observed to be dehydrated, alert, agitated, and

acutely ill. Blood pressure was 170/90 mm of mercury, the pulse 100 per minute and irregular, and the temperature 37.2°C (99°F). Neck veins were not distended. No rales or ronchi were noted on auscultation of the lungs. A holosystolic murmur was heard loudest at the cardiac apex with radiation to the left sternal border and left axilla. The abdomen was soft and not distended, but there was moderate diffuse tenderness and voluntary guarding on palpation. No masses or visceromegaly were noted. Bowel sounds were absent. The rectal ampulla contained 4+ hematest-positive stool. The extremities were cool without cyanosis or edema. Peripheral pulses were palpable. There were no petechiae or ecchymoses and the remainder of the physical examination was within normal limits.

Laboratory data on admission were: hematocrit 56 percent, hemoglobin 19.2 grams per 100 ml, leukocytes 29,300 per cu mm with a pronounced shift to the left. The serum electrolytes were: sodium 110, potassium 6.7 and chloride 78 mEq per liter. Blood urea nitrogen was 60 mg per 100 ml and creatinine was within normal limits, as was serum amylase. Results of urinalysis were normal. The platelet count was 35,000 per cu mm and the fibrinogen screen was 250 to 300 mg per 100 ml. Partial thromboplastin time, prothrombin time and thrombin time were all normal. Roentgenograms of the chest showed no acute pulmonary disease and the cardiac silhouette was normal. Radiographic films of the abdomen in the supine and erect positions demonstrated normal intestinal gas pattern with no signs of ileus. An electrocardiogram showed a high degree of atrioventricular block with periods of 2:1 block and atrioventricular dissociation. The intraventricular conduction defect along with diffuse ST segment depression was compatible with digitalis toxicity.

During the three hours following admission, the abdominal pain continued to be severe, generalized, and intermittent. A nasogastric tube was placed and 500 ml of "coffee ground" fluid was aspirated. A diagnosis of mesenteric thrombosis was subsequently made, and, after appropriate preoperative preparation, diagnostic celiotomy was carried out.

Exploration of the abdomen showed the small intestine, from the ligament of Treitz to the ileocecal valve, thickened and violaceous in some segments, while normal in others. No peristalsis was evident. In none of the involved segments did the bowel appear to be gangrenous. The mesenteric arterial system was pulsating throughout, with no demonstrable occlusion. The mesenteric venous system also appeared to be patent and without engorgement. Frozen section histologic examination of a wedge biopsy specimen of the jejunum taken from a decidedly discolored area showed necrosis of the mucosa, engorgement of the submucosal vessels and a normal muscularis and serosa (Figure 1). The pathologic diagnosis was hemorrhagic enteropathy of the small bowel. Massive resection of the small bowel was decided against, and the abdomen was closed.

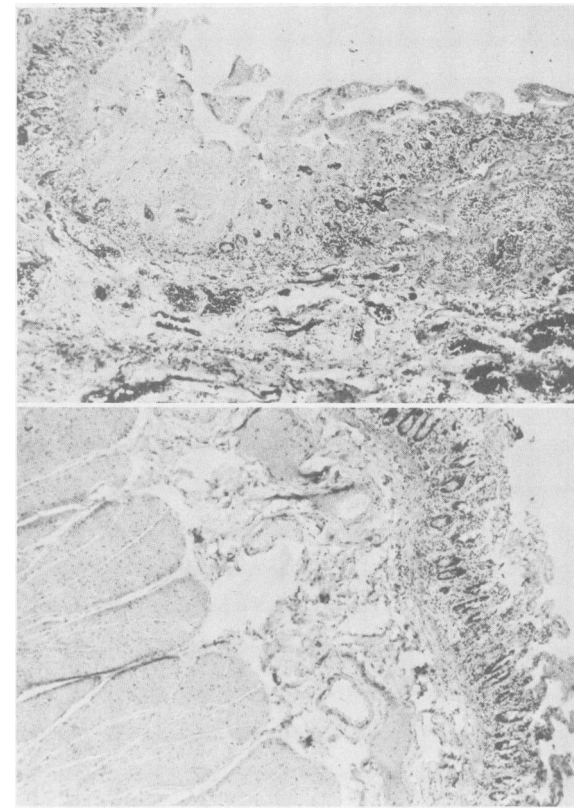

Figure 1.—Section of diseased small bowel demonstrating (in top frame) distortion of the mucosal architecture, engorgement of the mucosal and submucosal veins and (in lower frame) little or no involvement of the muscularis.

Postoperatively, penicillin and kanamycin were administered. Heparin and low molecular weight dextran were also given to prevent thrombosis of mesenteric vessels. Sixteen liters of intravenous fluid including colloid were required during the first 48 hours to maintain the vital signs within normal limits and an adequate urinary output.

On the third postoperative day significant respiratory distress developed. Roentgenograms of the chest showed a collapsed right upper lobe and

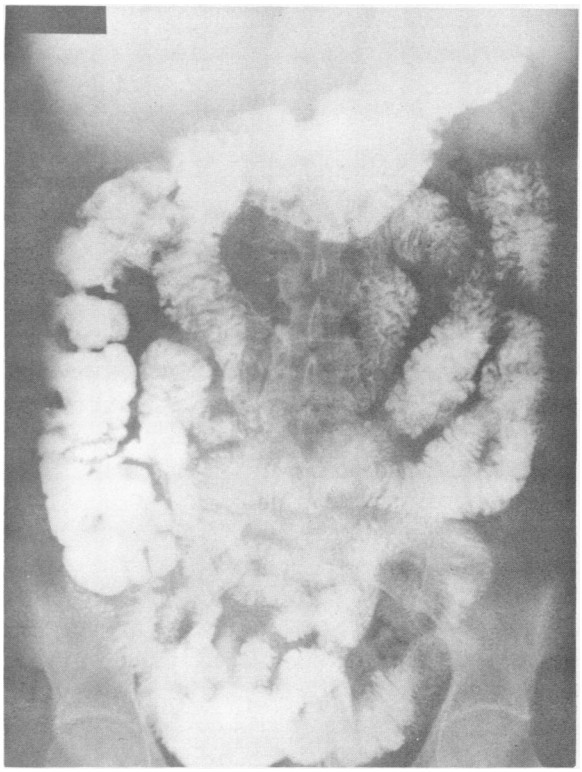

Figure 2.—Upper gastrointestinal x-ray study on the eighteenth postoperative day. The distal small bowel shows changes consistent with submucosal edema or hemorrhage.

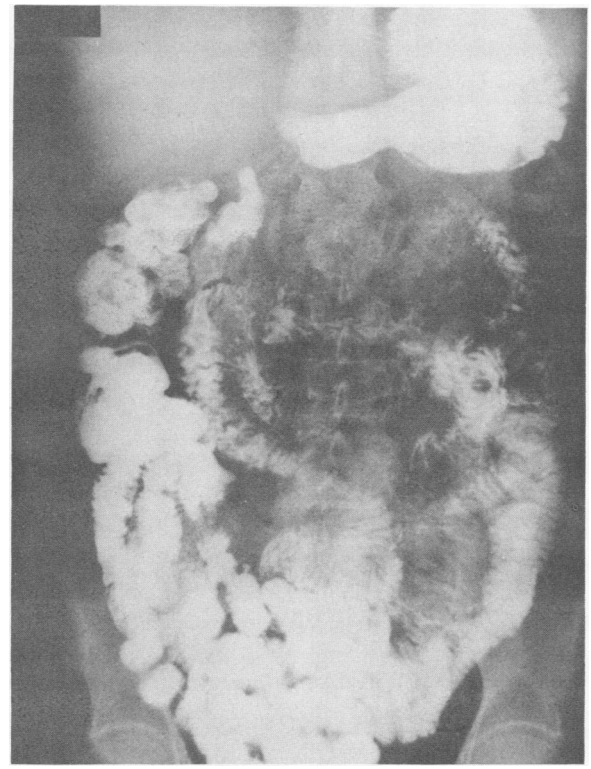

Figure 3.—An upper gastrointestinal study on thirty-fifth postoperative day showed complete resolution of earlier changes.

diffuse bilateral interstitial infiltrates. Tracheostomy was carried out. The patient was placed on a volume respirator and gradual improvement was noted. Oral intake was started on the seventh postoperative day and consisted of clear fluids, a magnesium-aluminum hydroxide suspension and Lactinex®.* An electrocardiogram showed normal sinus rhythm, and the ST segments were returning to baseline. By the twelfth postoperative day the patient had been advanced to a bland diet. Clinically and radiologically the lungs showed pronounced improvement. Laboratory data were normal with the exception of a hematocrit which remained at 30 to 32 percent. An upper gastrointestinal series with small bowel follow-through was obtained on the eighteenth postoperative day (Figure 2). The proximal small bowel appeared normal. There were changes in the distal small bowel consistent with submucosa edema or hemorrhage.

The patient was discharged on the twenty-first postoperative day. An upper gastrointestinal series two weeks after discharge showed complete resolution of the above findings (Figure 3). In six months of follow-up no symptoms referrable to the gastrointestinal tract occurred.

*A mixed culture of lactobacillus acidophilus and lactobacillus bulgaricus.

Discussion

Hemorrhagic necrosis of the gastrointestinal tract without the presence of demonstrable vascular occlusion has been the subject of numerous case reports over the last 15 years. In 1954, Wilson and Qualheim[13] described a diffuse hemorrhagic process involving the intestinal mucosa in which no vascular occlusion could be found. In 17 of their 20 reported cases the patients had chronic heart disease with varying degrees of congestive heart failure. A close relationship was noted between the onset of abdominal signs and symptoms and the treatment of congestive heart failure with digitalis but an etiologic role was not attributed to this drug. Ende[5] reported six cases of bowel infarction in which no significant mesenteric vascular lesions could be found. All of these patients had definite cardiac failure and were receiving digitalis preparations.

Kligerman and Vidone[7] reviewed all reported

cases of nonocclusive hemorrhagic necrosis of the intestine in the literature and added nine for a total of 109 cases. Cardiovascular disease and a history of congestive heart failure were present in 86 percent of these patients. A review of the individual series contributing to the total number of cases reported by Kligerman and Vidone disclosed that the majority of patients were taking digitalis.[1,3-6,8,13,16]

Musta[9] reported 31 cases of intestinal infarction without vascular occlusion. In 30 of them the patients had heart disease and 25 had chronic congestive failure. Ming[8] found that in his series of 75 patients with hemorrhagic necrosis of the intestine, 79 percent had heart disease with varying degrees of failure. Fifty-seven patients had been digitalized. Williams et al[12] presented seven cases, in six of which the patients had generalized arteriosclerosis and heart disease. Five were taking digitalis and digitalis toxicity was present in one. Sixteen cases were reported by Sorensen and Vetner[11] in 1969. Thirteen were in congestive heart failure and all were receiving digitalis. Digitalis intoxication was present in four.

Gazes et al in 1961 postulated a relationship of nonocclusive mesenteric infarction and digitalis.[16] They reviewed 11 cases and found that all of the patients had heart disease and had received large doses of digitalis. Several were in digitalis toxicity. Stating that the degree of cardiac decompensation varied significantly and conjecturing that if congestive heart failure were the primary cause of this lesion it would undoubtedly be seen more often, Gazes suggested that the "common denominator" was digitalization and digitalis toxicity. In 1964, Polansky and coworkers[18] reported 23 cases of nonocclusive infarction and in 21 of them the patients had mild to severe cardiac failure and were taking digitalis. Twelve patients were definitely in digitalis toxicity, and conditions suggestive of toxicity were present in seven others. They also postulated that digitalis toxicity appears to play an important etiologic role in mesenteric infarction without vascular occlusion.

Fogarty and Fletcher[15] compared the clinical features associated with the 102 cases of mesenteric occlusion with infarction with 18 cases of mesenteric infarction in which no vascular occlusion could be found. A "diagnostic triad" was noted that allowed the two entities to be differentiated. Nonocclusive mesenteric ischemia and infarction were associated with severe congestive heart failure in 89 percent of the cases while digitalis intoxication was present in 83 percent, and hemoconcentration also present in 83 percent. When ischemia and infarction are due to documented vascular occlusion, the figures are 16 percent, 13 percent and 21 percent, respectively. Muggia,[17] also in 1966, reported 11 additional cases of hemorrhagic necrosis of the intestine. All the patients were taking digitalis and eight of them had electrocardiographic changes consistent with digitalis toxicity. Muggia expressed belief that digitalis was an important contributory factor in infarction of the bowel without vascular occlusion and that this was primarily due to a direct effect of digitalis on the mesenteric vessels.

Pierce and Brokenbrough[10] reviewed 140 cases of mesenteric infarction, both occlusive and nonocclusive, and in each group found evidence of cardiovascular disease in 90 percent and low cardiac output in 50 percent. Digitalis was being taken by 90 percent of the patients without mesenteric arterial occlusion compared with 60 percent of those with occlusion. Digitalis intoxication was present in 27 percent without occlusion and in 9 percent with occlusion.

Clinical and pathologic features. The clinical and pathologic findings in all of these cases are similar. The clinical situation is that of a patient in the seventh or eighth decade with cardiovascular disease and congestive heart failure who has sudden onset of severe abdominal pain. Often there is a history of vague prodromal abdominal complaints. Abdominal tenderness, distension, nausea, vomiting and melena are usually present. The severity of the pain is generally out of proportion to the physical findings. Fever and leukocytosis are invariably present. A hematocrit greater than 50 percent is not uncommon, but this will depend on the amount of third space fluid loss and gastrointestinal hemorrhage. Abdominal x-ray films are of minimal value, with signs of mild ileus often being the only demonstrable findings. Abdominal angiography has been advocated by several observers.[13,19] Its primary value, however, has been in helping to explain the pathogenesis of this entity. A positive diagnosis cannot be made by arteriography, though it may be suggested by unequal flow patterns in the mesenteric vessels. All patients should have emergency elective angiography, if possible, to exclude occlusion of the major vessels. The clinical course is rapidly fatal, with shock usually the terminal event. There have

been no previously reported survivors of massive nonocclusive mesenteric infarction.

The small and large intestine at celiotomy or autopsy appear discolored, edematous and dilated. The mucosa is thin, friable and hemorrhagic, with superficial ulcerations often present in the most affected areas. The distribution may be diffuse or segmental and it bears no relationship to the major arterial supply. Arteriosclerotic involvement of the mesenteric vessels is common, but no point of arterial or venous occlusion is evident. Microscopically there is hemorrhage into the mucosa of the bowel, various stages of necrosis ranging from simple distortion of neutrophilic response, engorgement of the mucosal and submucosal veins, and little or no involvement of the muscularis propria and serosa.

Etiology. Hemorrhagic necrosis of the bowel without vascular occlusion is a common finding in dogs dying of hemorrhagic shock. When an animal is bled to a mean arterial pressure of 33 mm of mercury and the pressure is maintained at that level for at least four hours, circulatory failure and death occur.[20] At necropsy, the small bowel mucosa is ulcerated and necrotic. The mechanism producing these lesions in shock states of whatever cause is a stimulation of the sympathetic nervous system due to baroreceptor activity resulting in the release of norepinephrine at postganglionic nerve endings in the skin and viscera. Cutaneous and visceral vasoconstriction subsequently produces a decrease in the size of the circulating vascular space and an increase in total peripheral resistance. Continuing blood flow to the brain and heart is maintained. Prolonged vasoconstriction of the visceral bed ultimately leads to ischemic and tissue necrosis. Approximately 65 perecnt of the total blood flow to the intestinal wall is to the metabolically active mucosa.[21] Severe ischemia consequently produces extensive damage to the bowel mucosal. The canine hepatic venous response secondary to sympathomimetic stimuli is very prominent because of smooth muscular fibrils in the hepatic veins which act as a sphincteric mechanism. Constriction of these muscles produces a noticeable increase in portal venous pressure, which causes mesenteric congestion.[20] Corday and coworkers[3] conducted a series of experiments to determine whether mesenteric or hepatic angiospasm was responsible for the canine gastrointestinal ischemia and necrosis seen in low flow states. They found that during acute hypotension and arrythmias, angiospasm of the mesenteric arterioles occurs and portal venous pressure decreases, suggesting that spasm of the hepatic veins does not play a significant role in producing bowel necrosis. They concluded that with congestive heart failure and cardiac arrythmias, the cardiac output is diminished and hypotension develops. The result is a compensatory vasoconstriction which may be severe enough to cause intestinal infarction.

Humans with nonocclusive intestinal infarction show a variable degree of congestive heart failure at the onset of abdominal complaints. Although most such patients have heart disease with a history of failure, few are actually in severe failure when infarction occurs. It is this fact that has led several investigators to postulate that, in addition to a low cardiac output, an arteriosclerotic and already compromised mesenteric vasculature must exist for nonocclusive infarction to take place.[5,7,15]

The law of La Place has been offered as a possible explanation for the diminished splanchnic blood flow which leads to mesenteric infarction without occlusion.[6] This physical law relates total tension in a vessel wall to its radius and the hydrostatic pressure within it. The important physiologic implication is that blood vessels under vasomotor tone have a "critical closing pressure." If the pressure in the arterioles of a vascular bed falls below this critical pressure, there will be an abrupt cessation of all blood flow. This is presumed to be the mechanism in the arterioles of the mesenteric vascular bed and results in ischemia with ultimate progression to infarction.

The time at which the patients with nonocclusive hemorrhagic necrosis present in clinical shock is variable. In some cases the onset of shock follows the appearance of abdominal pain, while, in others, it is a terminal event or does not occur at all. Only one of the 11 patients reported by Ming[8] was in shock before the onset of abdominal pain. Musa[9] observed that shock was present in only 16 of 31 patients, seven of whom had abdominal signs and symptoms before the onset of shock. Shock was the initial event in nine instances. Theoretically, any type of vascular collapse with compensatory vasoconstriction may precipitate bowel ischemia and infarction. However, Musa concluded that in humans there must be pre-existing cardiac disease.

Fogarty and Fletcher[15] noted three persistent findings in nonocclusive mesenteric ischemia—

severe congestive heart failure, hemoconcentration, and digitalis intoxication. They suggested that these factors might be etiologically related to the development of the disease. Because of vomiting and third-space fluid loss, the hematocrit of these patients is usually high. Elevation of the hematocrit in the face of vasoconstricted and arteriosclerotic vessels offers a significant resistance to flow and may lead to ischemia.

The extracardiac manifestations of digitalis have been the subject of several investigations. The peripheral vascular effects of digitalis were studied by Ross et al.[21,22] By removing the heart from the circulation and thereby eliminating the positive inotropic effect of the drug from consideration, significant arterial and venous vasoconstriction was demonstrated through use of therapeutic doses of digitalis. Ganglionic blockade or adrenalectomy did not prevent this response. They concluded digitalis has a direct action on vascular smooth muscle which results in both arterial and venous vasoconstriction. Using a patient on cardiopulmonary bypass, Braunwald and coworkers[23] studied the effects of digitalis on systemic vascular resistance and confirmed these direct systemic vasoconstriction properties in man. Mason and Braunwald,[24] also studying the effects of digitalis on forearm vascular resistance and venous tone in normal subjects, demonstrated a direct constricting action of digitalis on forearm vasculature in normal subjects.

Ferrer et al[25] found an intensification of splanchnic vasoconstriction following digitalis therapy in patients with ventricular failure. Mason, however, repeating his digitalis studies on forearm vascular resistance in patients who were in heart failure, showed decreased vascular tone and increased blood flow secondary to the digitalis-induced improvement in cardiac output, and subsequent decrease in reflex arteriolar and venoconstriction. This vasodilatory action is indirect and apparently overrides the direct vasoconstrictor effect. This improvement in myocardial contractility and cardiac output does not overcome the splanchnic vasoconstriction demonstrated by Ferrer et al. They postulated that the "splanchnic vasoconstrictor driver of failure" may be altered by a mechanism other than the baroreceptor system or that digitalis has a selective vasoconstrictor effect on the splanchnic vessels.

Corday et al[3] showed that cardiac arrythmia in dogs can produce mesenteric ischemia by lowering cardiac output and initiating a compensatory vasoconstriction. Since arrythmia is intimately associated with digitalis toxicity, this may be one of the ways in which digitalis intoxication produces mesenteric ischemia. This indirect mechanism is probably not as significant as the direct vasoconstrictor action on the splanchnic vessels.

The digitalis intoxication seen in the case herein reported could have produced nonocclusive mesenteric infarction in several ways. There was a three-day history of persistent vomiting, initially due to the well known central effect of digitalis, leading to dehydration and hemoconcentration resulting in an increased resistance to mesenteric flow. The cardiac arrythmia secondary to intoxication along with the contracted blood volume resulted in decreased cardiac output and compensatory vasoconstriction. Finally, and perhaps most important, was the direct vasoconstrictor action of digitalis intensified by the toxic dose. Each one of these factors, as well as some degree of preexisting congestive heart failure, contributed to the massive nonocclusive mesenteric infarction seen in this case. All of these factors are of significance in the development of this entity. The role of each differs from case to case. It is questionable whether any of these factors alone could produce nonocclusive hemorrhagic necrosis in man. It is important not only to recognize that such a lesion exists, but to understand the circumstances in which it occurs.

Treatment

Successful treatment is based upon early recognition and nonoperative management. Early diagnosis was the major factor in the survival of the patient reported here. Celiotomy should be avoided and the diagnosis made on clinical grounds, but it is often a difficult task to differentiate between occlusive and nonocclusive infarction without the benefit of intraoperative examination. Abdominal selective angiography may be of help in this situation. Should celiotomy be carried out and no point of vascular obstruction demonstrated, a thorough knowledge of the disorder will prevent fruitless, prolonged search and needless resection.

Nonoperative management includes close monitoring of the blood pressure, pulse rate, urine output, central venous pressure, and hematocrit. All fluid losses should be immediately replaced with the appropriate intravenous solutions. Hemoconcentration must be corrected. Low modecular

weight dextran or heparin or both are suggested as a means of enhancing mesenteric blood flow.

The use of vasoactive drugs has been proposed in a number of reports.[2,12,20] Circulatory support through the use of vasopressors such as norepinephrine is inconsistent with what is known of the pathophysiology of nonocclusive mesenteric infarction. Vasoconstriction of whatever cause is widely accepted as the precipitating event. Any agent that increases splanchnic vasoconstriction is detrimental to the survival of the bowel. Isoproteronol, a beta adrenergic stimulating agent, and phenoxybenzamine, an alpha adrenergic blocking agent, have been considered efficacious in the treatment of low output shock, as their effect is to increase cardiac output. These agents should never be used instead of or before aggressive fluid replacement. Intravenous fluid replacement, closely monitored with central venous pressure or pulmonary artery wedge pressure, is necessary for survival and is indicated even in the face of a history of cardiac decompensation.

Many of the patients are taking digitalis. It is important to realize that increasing the dose or giving additional doses in an effort to improve myocardial contractility can easily result in toxicity because of the pronounced fluid and electrolyte shifts associated with mesenteric infarction. Because of this and reports linking digitalis and its direct peripheral vasoconstriction to nonocclusive mesenteric infarction, discontinuation of digitalis therapy should be strongly considered. If toxicity is present, it should be promptly treated.

Finally, broad spectrum antibiotic coverage is essential because of the necrotic state of the intestinal mucosa. The mucosal barrier has been destroyed, leaving these patients very susceptible to massive sepsis.

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